



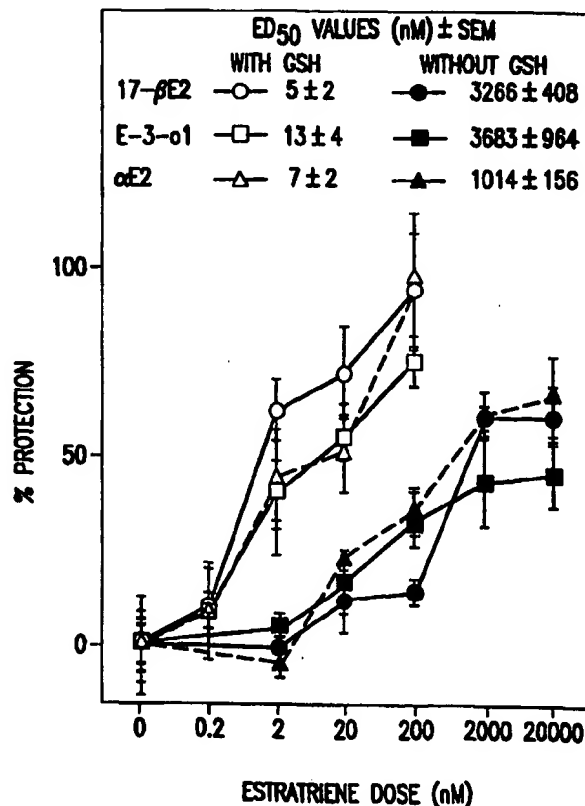
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(54) Title: COMPOSITIONS TO ENHANCE THE CYTOPROTECTIVE EFFECTS OF POLYCYCLIC PHENOLIC COMPOUNDS THROUGH THE SYNERGISTIC INTERACTION WITH ANTI-OXIDANTS

(57) Abstract

A method is provided for enhancing the cytoprotective effect of polycyclic phenolic compounds on a population of cells that involves the steps of administering a combination of polycyclic phenolic compounds and anti-oxidants to achieve an enhanced effect that is greater than the use of either compound administered separately under otherwise similar conditions. An example of an anti-oxidant for use in the method is glutathione and an example of a polycyclic phenolic compound is an estrogen compound. The cytoprotective effect occurs in a variety of different cell types including neuronal cells and cells of the vascular system.



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COMPOSITIONS TO ENHANCE THE CYTOPROTECTIVE EFFECTS OF POLYCYCLIC PHENOLIC COMPOUNDS
THROUGH THE SYNERGISTIC INTERACTION WITH ANTI-OXIDANTS

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Background

10 There is a need for treatments that protect cells from cell death resulting from
episodes of disease, trauma, isolation and removal of tissues or cells from the body, or
exposure to toxins. This need extends to treatments for nerve cell loss associated with
chronic or acute neurodegenerative disorders or trauma; treatments to minimize tissue
damage resulting from ischemia where ischemia may occur as a result of stroke, heart disease,
15 a transplantation event, or other event resulting in a cut-off in nutritional supply to tissues;
and treatment to modulate cell death associated with conditions such as osteoporosis or
anemia. The absence of an effective cytoprotective therapy can result in either loss of life or a
general decline in the quality of life including permanent disability with high health care costs
to patients, their families and the health care providers. One approach to minimize pathologic
20 changes has been to attempt to neutralize the oxidative stress that is associated with an
accumulation of free radicals in the extracellular space. Mooradian, J. Steroid Biochem.
Molec. Biol. 45 (1993) 509-511 has reported that certain estrogens have significant anti-
oxidant properties in *in vitro* biochemical assays but this effect is not seen with all estrogens.
Because of the variation in anti-oxidant properties noted by Mooradian in his biochemical
25 assays, he concluded that steroid molecules must have certain anti-oxidant determinants
which were as yet unknown. Similar observations concerning steroids with phenolic A rings
were reported in WO 95/13076 using biochemical assays to show anti-oxidant activity. The
assays used by Mooradian and by WO 95/13076 were biochemical assays and as such did not
directly examine the effects on cells of these molecules. US 5,554,601 (1996) however
30 described cell based assays to determine a method of conferring neuroprotection on a
population of cells using estrogen compounds based on demonstrated cell protective effects.

Oxidative damage has been associated with a variety of neurodegenerative diseases including Alzheimer's disease (AD); and the aging process. (Benzi et al. Free Radic. Biol. Med. 19, (1995); 77-101, and US 5,554,601 incorporated herein by reference) . Cell death also occurs following an ischemic event in the body resulting from nutrient deprivation which may be associated with oxygen deprivation resulting from an occlusion in a cerebrovascular or cardiovascular location or may be associated with trauma or disease.

There is a need for improved methods of protecting both men and women from the consequences of abnormal cell death in body tissues.

Summary

In an embodiment of the invention, a method is provided for conferring cytoprotection on a population of cells that includes providing a polycyclic phenol compound, and an anti-oxidant compound; and administering the polycyclic phenol compound and the anti-oxidant compound to the population of cells at an effective dose so as to confer cytoprotection such that the combined cytoprotective effect of the polycyclic phenolic compound and the anti-oxidant compound is greater than the additive effect of each compound administered separately under otherwise similar conditions.

A further embodiment of the invention is a method of conferring cytoprotection on a population of cells in a subject, including the steps of providing a combination therapeutic dose containing an anti-oxidant and a polycyclic phenolic compound in a pharmaceutical formulation; administering the formulation in an effective dose to the population of cells such that the cytoprotective effect of the combination in the subject is greater than the additive effect of each compound provided separately; and protecting cells in the subject that would otherwise deteriorate and die in the absence of the pharmaceutical formulation.

In further embodiments of the invention, the combined effect may be a 100-10,000 fold enhancement, more particularly a 100- 5,000 fold enhancement, more particularly a 1,000-5,000 fold enhancement of cytoprotection resulting from the combined effect of the polycyclic compound and the anti-oxidant compared with each compound separately. In further embodiments of the invention, the polycyclic phenol compound is an estrogen compound more particularly an estrogen compound having insubstantial sex activity